## REMARKS

**Rejection under 35 U.S.C. § 112, first paragraph**

In the October 2, 2001 Office Action, claims 1-54 were rejected under 35 U.S.C. §112, first paragraph. The only issue raised in the October 2, 2001 Office Action is one of enablement. This rejection is hereby traversed and reconsideration of the patentability of the pending claims, as amended herein, is requested in light of the following remarks.

The Office stated that the specification, "while being enabling for *in vitro* anti-HIV activity, does not reasonably provide enablement for preventing HIV infection or replication in a human subject." Applicants vigorously disagree. Initially, the Office has not specifically provided a basis for its reasoning that the disclosure is insufficient to support applicants' claimed compounds and uses. Without such basis, the rejection of the claims under Section 112, first paragraph for lack of enablement is contrary to well established law. (*Ex parte Kenaga*, 189 USPQ 62 (BPAI 1974)).

Applicants remind the Office that the standard for enablement and thus patentability is not the same as that required for drug marketing approval by the Federal Drug Administration. See *Scott v. Finney*, 32 USPQ2d 115 (Fed. Cir. 1994). Patentability and enablement do not hinge on the outcome of human clinical trials. The Office has faulted the applicants for not providing *in vivo* examples to show the efficacy of the claimed invention in human subjects. Applicants submit that the efficacy of the compositions of this invention is fully and rigorously established by applicants' empirical determinations — applicants tested the efficacy of the claimed compositions *in vitro* to determine the positive results showing anti-HIV activity.

Positive correlation for effective results between *in vitro* and *in vivo* testing of HIV therapies is well known to those skilled in the art and exemplified in several references provided by applicants and included in Appendix C. Specifically, Dr. Martin Hirsch (The AIDs Reader 7(4): 116-119 (1997), see page 3 of printout) discussed that early *in vitro* studies demonstrating the effectiveness of combination treatments for HIV were confirmed by clinical studies 5 years later. Also, AZT treatments demonstrated close agreement between *in vitro* and *in vivo* testing. AZT testing had been evaluated *in vitro* by several laboratories, and the *in vitro* data showed good inter-laboratory reproducibility and agreed well with the *in vivo* data. Further, there was considerable agreement between the active range of concentrations *in*

*vitro* and *in vivo*, despite the fact that the methodology had not been optimized for undertaking such comparison. (see Gribaldo, et al. "The Use of *In Vitro* Systems for Evaluating Haematotoxicity" (1995), see page 11 and 12 of printout). Yarchoan and Broder (page 101, second sentence in second full paragraph) states in a discussion related to AZT that "the drug levels associated with clinical activity were consistent with those that had anti-HIV activity *in vitro*." Yarchoan and Broder (1992) *J. Enzyme Inhibition* 6: 99-111. These references demonstrate the utility of *in vitro* test data in predicting *in vivo* clinical test results.

The Board of Patent Appeals and Interference addressed this issue of correlation between *in vitro and in vivo* testing results in *Ex Parte Balzarine*, 21 U.S.P.Q.2d 1892 (BPAI 1991) wherein the examiner cited a 1987 reference by Yarchoan, et al. as proof that there was no correlation between *in vitro* and *in vivo* testing results. However, the Board stated that the appellant could provide evidence that established that those skilled in the art would accept that *in vitro* testing would be useful in *in vivo* treatment of humans afflicted with HIV or AIDs. In the present case, applicants have met this burden and presented ample proof of a positive correlation between *in vitro* and *in vivo* testing results for HIV treatments, as recognized by those skilled in the art.

The Office further contends that "Applicant has not provided any evidence that their system would work as a preventing method, lacking any convincing evidence to the contrary." Thus, the Office seems to suggest that this enablement rejection may be overcome by presenting evidence that disclosed *in vitro* models will correlate with *in vivo* efficacy in testing subjects.

Subsequent to the applicants' filing date, several articles have been published that provide further validation and corroborative evidence that applicant's claimed invention exhibits anti-HIV activity not only *in vitro* but also *in vivo*.

For example, Mosier et al.[2] found that AOP-RANTES and NNY-RANTES, analogs of RANTES, inhibited virus infection *in vitro* . More important, the anti-HIV activity was confirmed in *in vivo* testing. Specifically the AOP-RANTES and NNY-RANTES were administered to hu-PBL-SCID mice. Tests conducted with the AOP-RANTES chemokine, at concentration levels found to be completely inhibitory *in vitro*, were administered to four mice. It was found that two of the four mice that were injected with AOP-RANTES had undetectable viral RNA levels at the end of a 7-day infusion period. Once infusion

[2] Mosier et al. *J. Virol.* 73(5):3544-50 (1999).

was ceased the virus returned. However, the results provide ample evidence that administration of a chemokine compound effected a **reduced viral load,** if not a full inhibitory response.

The ***in vivo*** inhibitory capacity of NNY-RANTES was also tested. The NNY-RANTES chemokine was administered at a concentration level less than that found to be effective in *in vitro* tests. The Mosier group found that four of the five mice infused with the chemokine, at these lower concentration levels, had an undetectable viral RNA level after the 7-day infusion period. After infusion ceased, only one of the four viral free animals reverted. The test was repeated, and the overall results showed that ***in vivo*** administration of NNY-RANTES was able to prevent HIV-1 infection in 6 of 10 hu-PBL-SCID mice at plasma concentrations lower than the 50% inhibitory does for HIV-1 *in vitro*. Thus, this positive correlation between *in vitro* and *in vivo* results further corroborates the efficacy of applicants' claimed invention for using chemokines that block HIV-1 coreceptors for an effective anti-HIV therapy.

**Lu et al., Clin. & Exp. Immun. 1999 Feb; 115 (2): 335.**

Lu, et al., showed that ***in vivo*** administration of the MIP-1α chemokine suppressed the growth activity of HIV. The Lu group linked a nucleotide sequence that codes for **MIP-1α** with the HIV *env* gene in a plasmid. The MIP-1α containing plasmid induced an increased humoral and cellular immune response in inoculated mice, relative to mice inoculated with only the HIV gene. Further, it was found by the Lu group that injection with the **MIP-1α encoding sequence suppressed the growth of HIV**. The emphasis of the study was to examine the immune modifications elicited by MIP-1α expression plasmid. It was found that co-inoculating immunogenic DNA with MIP-1α augmented the potency of the DNA vaccinations. Moreover, the IgG1/IgG2a ratio was significantly lower than that obtained using the DNA vaccine alone, suggesting activation of Th 1-type cells . Activation of a Th1-type immune response is vital for HIV-1 protection and therapeutic efficacy. The results described in Lu reference further demonstrated that injection with MIP-1α caused massive inflammatory infiltration in the injected site. Thus, in addition to the adjuvant activity, MIP-1α suppressed the growth of HIV, possibly by interfering with HIV binding to CC-CKR3 and CC-CKR5 as contemplated by the researchers.

**Lehner et al., Immun., 2000; 99; 569-577**

The object of the Lehner study was to evaluate if human immunodeficiency virus-1 (HIV-1) infection involves up-regulation of β-chemokines, which bind and may down-modulate the CCR5 co-receptors, thereby preventing transmission of M-tropic HIV-1 *in vivo* in non-human primates. The investigation was based on the premise that *in vivo* immunization with SIV antigens, with or without cytokines, may in

addition to specific immunity to SIV, up regulate CD8-SF and elicit innate immune response by generating β-chemokines that block and down-modulate CCR5 thereby decreasing SIV transmission. The results of the plasma SIV mac RNA showed a significant inverse correlation with CD8-SF and the β-chemokines, but a positive correlation between the proportion of CCR5+ cells and SIV mac RNA. This result demonstrated that ***in vivo*** immunization up-regulates β-chemokines which may down-modulate CCR5 co-receptors, and both functions are significantly correlated with the viral load.

**Ferbas, et al., Jour. Inf. Dis., 2000 Aug; 182: 1247-1250**

Results showed that levels of RANTES, MIP-1α and MIP-1β produced in response to stimulation with HIV proteins was significantly associated with reduced viral replication ***in vivo***. RANTES, MIP-1α and MIP-1β production ***in vitro***, therefore, appears to be a correlate of immunity in the HIV model. The data provides evidence for a significant inverse correlation between antigen-stimulated augmented RANTES, MIP-1α and MIP-1β production and reduced *in vivo* burden. The investigators further concluded that augmenting production of RANTES, MIP-1α and MIP-1β may limit viral replication *in vivo*, thereby reducing destruction of host $CD4^+$ T cells.

**Genin et al. Virology 1999 Sep 1; 261 (2): 205-15**

The importance of chemokine expression on HIV infection has been emphasized by the discovery that infection of CD4(+) T cells by M-tropic strains of HIV-1 is antagonized by the chemokines RANTES, MIP-1α and MIP-1β which are natural ligands of CCR5, a major coreceptor for macrophagetropic (M-tropic) isolates of HIV-1. Similarly, the ligands MCP-1 and MCP-3 inhibit productive infection of PBMCs by both CCR5 and CXCR4-dependent strains of HIV-1, suggesting that MCP-1 may affect HIV infection via signaling through the CCR2 receptor and subsequent desensitization of the CCR5 and/or CXCR4 signaling pathway.

**Greco et al. J. Gen. Virol. 1999 Sep; 80 ( Pt 9): 2369-73**

Examination of a large panel of chemokines indicated that in addition to RANTES, MIP-1α and MIP-1β, the beta-chemokine MCP-2 and, to a lesser extent, the gamma-chemokine lymphotactin also showed anti-human immunodeficiency virus (HIV) activity in cell culture.

**Gong et al. J. Biol. Chem. 1998 Feb 20; 273 (8): 4289-92**

The study showed that MCP-2 inhibited the entry/replication of $HIV\text{-}1_{ADA}$ in CCR5/293 cells coexpressing CD4. This result indicates that MCP-2 uses CCR5 as one of its functional receptors and is

an additional potent natural inhibitor of HIV-1 natural inhibitor of $CD4^+$/CCR5-mediated HIV-1 entry/replication in host cells in addition to MIP-1α, MIP-1β and RANTES.

**Horuk et al., J. Biol. Chem. 1998 Jan: 273: 386-391**

Horuk et al. confirmed that the CC chemokine I-309 can inhibit HIV: It was shown that CCR8 is a coreceptor for HIV-1 and that I-309 potently inhibited both HIV-1 envelope-mediated cell-cell fusion and virus infection of cells expressing $CD4^+$ and CCR8.

Thus, the results described in the above-discussed references underscore the fact that applicants' disclosure was in fact enabling when filed. Further, the results provide corroborative evidence to convince one skilled in the art that the chemokine compounds and their use, within the scope of applicants' claims, exhibit significant anti-HIV activity both *in vitro* and *in vivo*. Applicants submit that the claims in the present application, as now amended, fully comply with all requirements under of 35 U.S.C. §112.

The pending claims recited in the present application have been compiled in groups to re-emphasize the patentability of each group.

**1. Method Claims for Formulating a Composition**

Claims 1-6 and 7 recite a method of **formulating a composition specific for a HIV-1 isolate** of an individual comprising one or more chemokines for use in a pharmaceutical composition that has anti-HIV activity in the isolate.

Claims 8-17 and 54 recite a method of **formulating a composition specific for a HIV-1 isolate** of an individual by assaying a chemokine for the ability to inhibit HIV infection, replication or expression of an RNA or a protein of HIV.

Claim 50 recite a method of **formulating a composition specific for one or more HIV-1 virus isolates** comprising contacting $CD4^+$ cells and the isolates with a chemokine in a first aliquot to determine reduction in virus load relative to an aliquot not contacted with a chemokine to determine the efficacy of the chemokine for use in a pharmaceutical composition to inhibit HIV infection or replication in CD4+ cells.

The applicants have provided detailed step-by-step instructions describing how to practice the invention. Support for the claimed processes for formulating a pharmaceutical can be found at pages 40 to 41 of the specification which generally includes:

isolating primary virus and/or HIV infected cells from a specific patient;

testing virus against panel of chemokines;

identifying chemokines having anti-HIV activity; and

preparing a formulation comprising such chemokines for administration to the specific patient.

Exemplary procedures for performing such assays are provided in Examples at pages 51-56 of the specification. Thus, the above-identified claims, directed to a method of formulating a composition, are fully enabled by the present specification and the specification provides reasonable detail to enable one skilled in the art to understand and carry out the invention.

**2. Method of Inhibiting HIV infection or replication in cells of a subject**

Claims 18-20 and 54 recite a **method of inhibiting HIV infection or replication in cells of a subject** by administering a pharmaceutical composition comprising at least one chemokine selected from a specific group.

Likewise, the specification provides ample guidance for claims directed to a method to inhibit HIV infection or replication for the same reasons as set forth in Group 1 claims.

**3. Method of Inhibiting HIV Infection or Replication in a subject**

Claims 22-23 and 28-30 recite **a method of inhibiting HIV infection or replication in a subject** by administering a pharmaceutical composition that includes a nucleotide sequence that encodes for at least one chemokine selected from a specific group.

Claim 37 recites a method of **a method of inhibiting HIV infection or replication in a subject** by administering a pharmaceutical composition that includes a first and second nucleotide sequence that encode for at least one chemokine selected from a specific group.

Claims 22-23, 28-30 and 37 are directed to a method of inhibiting HIV infection or replication in a subject.

Based on the disclosure in the application, the claimed compounds have a predictable efficacy for the following reasons:

applicants claim a limited group of chemokines whose utility can be easily verified according to the methodology set forth in the application;

the application contains a detailed methodology for identifying and verifying new compounds that will work; and

subsequent empirical work has confirmed the predicted efficacy.

The applicants have provided a detailed description for a novel method of preparing a novel pharmaceutical formulation comprising chemokines having specific utility to treat a subject having a specific HIV strain at a particular state of disease progression.

**4. Pharmaceutical compositions**

Claims 38-42 recites **a pharmaceutical composition comprising a chemokine** in an amount to inhibit HIV infection or replication in infected cells.

Claim 49 recites **a pharmaceutical composition comprising two or more chemokines** that bind to at least one chemokine receptor selected from a specific group of receptors.

Claim 51 recites **a pharmaceutical composition comprising MDC and I-309.**

One skilled in the art would be quite capable of making and using applicants' claimed compositions, and thus the composition claims meet the enablement requirements of Section 112, first paragraph.

It is well settled in the law that a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of Section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. The Office has not provided any evidence that one of ordinary skill in the art would doubt the objective truth of the statements contained in applicants' disclosure, and thus, all claims as now amended meet the requirements under 35 U.S.C. §112, first paragraph.

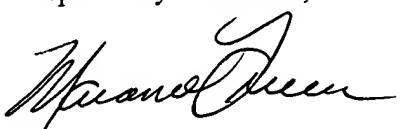
**Petition for Extension of Time/Fees Payable**

Applicants hereby petition for a one (1) month extension of time, extending the deadline for responding to the October 2, 2001 Office Action from January 2, 2002 to February 2, 2002. The entry of this petition results in a petition fee of $55.00. A check in the amount of $55.00 is submitted herewith in payment of the petition fee for a two month extension. The U.S. Patent and Trademark Office is hereby authorized to charge any additional amount necessary to the entry of this amendment, and to credit any excess payment, to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

**Conclusion**

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Park reconsider the patentability of claims 1-5, 7-20, 22-23, 28-30, 37-42, 49-51 and 54 in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Park is requested to contact the undersigned attorney at (919) 419-9350 to resolve same.

Respectfully submitted,



Marianne Fuierer
Registration No. 39,983
Attorney for Applicants

**INTELLECTUAL PROPERTY/**
**TECHNOLOGY LAW**
**P. O. Box 14329**
**Research Triangle Park, NC 27709**
**Phone: (919) 419-9350**
**Fax: (919) 419-9354**
**Attorney File: 4115-115 CIP**